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REGIOSELECTIVE SYNTHESIS OF 7,8-DIOXYGENATED-3,4-DIHYDROISOQUINOLINES BY METALATION OF ß-PHENETHYLAMINES

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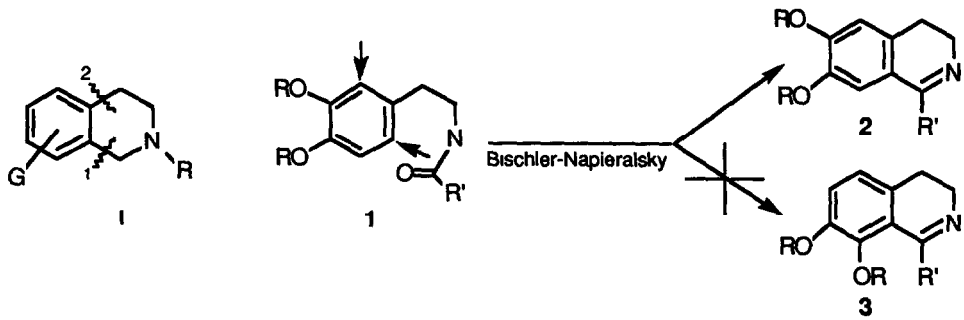
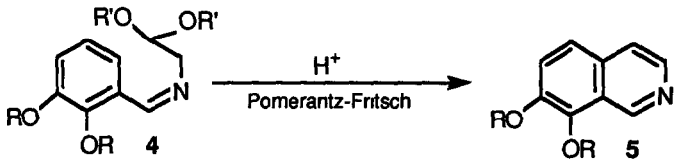
Summary: A new, one-pot procedure for the synthesis of the title compounds is described which is based on the thermodynamic metalation of the corresponding β-(3,4-dialkoxyphenyl)ethylamine

The tetrahydroisoquinoline unit **I** is present in a very large number of naturally occurring alkaloids, many of which are of pharmacological interest.[1] Although there are many different approaches to the synthesis of the isoquinoline nucleus,[2] the classical methods involving the Bischler-Napieralsky, Pictet-Spengler and Pomerantz-Fritsch reactions continue to be the most frequently used. The first two of these methods involve formation of bond 1 in structure **I** by electrophilic attack on the aromatic ring, and are hence strongly dependent on the position and nature of substituents.They are only suitable for the synthesis of isoquinolines which bear a strongly electron-releasing group *para* to the cyclization point This is the case in N-acyl-β-phenethylamines (**1**), which cyclize under the action of dehydrating agents to give good yields of 6,7-dialkoxy-3,4-dihydroisoquinolines (**2**), unmixed with the 7,8-dialkoxyderivatives (**3**) that result from attack *ortho* to the directing group. This latter type of isoquinolines can only be prepared by indirect methods consisting mainly in the blocking of the more reactive *para* position.

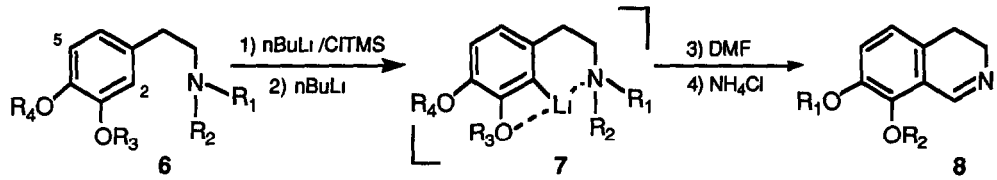


For the above reasons the Pomerantz-Fritsch reaction [formation of bond 2 in I] is the method of choice for the synthesis of 7,8-disubstituted isoquinolines, since in this case the fact the Schiff base **4** has only one position susceptible to electrophilic attack leads to exclusive formation of the isoquinoline **5**, though yields are often low due to competitive hydrolytic cleavage of the starting imine Several modifications have been introduced which improve the yield of the cyclization step, but they usually require more manipulation.[3]



Our current interest in the preparation of 7,8-dioxygenated isoquinolines, the type of substitution present in the cularine alkaloids,[4] has prompted us to study their synthesis from the readily available β-(3,4-dialkoxyphenyl)ethylamines (**6**), which in the classical Bischler-Napieralsky and Pictet-Spengler reactions give the undesired 6,7-disubstituted isoquinolines

We envisaged that regioselective metalation at C-2 in the β-phenethylamine **6** would provide us with the organometallic derivative **7**, and that trapping with DMF would then lead, after cyclization, to the desired 7,8-disubstituted-3,4-dihydroisoquinoline **8** Recent work by Liang [5] has shown that tetramethyldopamine (**6a**) undergoes kinetic metalation by alkyl-lithium at C-5, but upon standing at room temperature equilibrates to give the more stable organolithium **7a**



a $R_1=R_2=R_3=R_4=Me$
b $R_1=R_2=H$, $R_3=R_4=Me$
c $R_1=CHO$, $R_2=H$, $R_3=R_4=Me$
d $R_1+R_2=(Me)_2Si(CH_2)_2Si(Me)_2$, $R_3=R_4=Me$
e $R_1=R_2=H$, $R_3=CH_2OMe$, $R_4=Me$

a $R_1=R_2=Me$
b $R_1=Me$, $R_2=CH_2OMe$
c $R_1=Me$, $R_2=H$

With this precedent we first attempted metalation of the β-phenethylamine **6b** by nBuLi (2 eq) in THF at O°C followed by stirring at room temperature (16h) and quenching by DMF (2 5 eq.) The product (63%) was the N-formylderivative **6c**,[6] a result which can be attributed to the low solubility of the intermediate amide precluding metalation of the aromatic ring

In order to overcome this difficulty we decided to protect the free amine with an easily removable group which after metalation would break off during work-up to

give the desired 3,4-dihydroisoquinoline in a one-pot process. The protecting group selected was 1,2-bis(chlorodimethylsilyl)ethane,[7] which reacted with the primary amine **6b** (nBuLi, THF, r.t.) to give the cyclic disilylazane **6d** (90% yield). However metalation of this protected derivative [nBuLi(1 1eq.), ether, r.t , 16h] followed by addition of DMF (1.6eq.) and acidic work-up (10% HCl) did not give the desired isoquinoline [8] In contrast, "in situ" protection of the amine **6b** with 2 eq of ClTMS and nBuLi, followed by metalation in the above conditions, addition of DMF (1 1eq) and quenching with saturated aqueous ammonium chloride solution, gave directly the 7,8-dimethoxy-3,4-dihydroisoquinoline **8a**,[9] which was isolated by column chromatography in 45% yield The use of THF as solvent gave a similar yield (40%)

In an attempt to improve the yield by avoiding possible β-elimination in the side chain, we monoprotected **6b** by reacting the amine with 1 eq of ClTMS and 2 eq of nBuLi in order to have an N-silylamide that was expected to be less prone to elimination, but its subsequent metalation under the above conditions gave an unimproved 46% yield

We were next interested in checking the validity of the new method for the synthesis of isoquinolines that are phenolic at C-8, wich are needed in the synthesis of cularine alkaloids [4] To this end we selected the MOM-protected β-phenethylamine **6e** [10] in the expectation that the known "ortho-directing" ability of the methoxymethyl group would improve the yield of the metalation Protection of the amine **6e** with one equivalent of ClTMS followed by metalation with nBuLi (ether, r t , 3h) and quenching with DMF (1 1 eq) gave, after work-up by addition of ammonium chloride solution and isolation, a 36% yield of the 3,4-dihydroisoquinoline **8b** Deprotection (MeOH, conc HBr, r t) led to 8-hydroxy-7-methoxy-3,4-dihydroisoquinoline hydrobromide (**8c**) [9]

In conclusion, we have developed a one-pot procedure for the synthesis of 7,8-dioxygenated-3,4-dihydroisoquinolines from readily available β-(3,4-dialkoxyphenyl)ethylamines based on thermodynamic metalation at C-2 in the aromatic ring Although yields were low, this is the only direct procedure for preparing isoquinolines of type **8**, so it compares favourably with more indirect methods In addition, the described procedure can also be used for the preparation of 7,8-dioxygenated-tetrahydroisoquinolin-1-ones Thus, metalation under the general conditions of the bis(TMS) protected derivative of the amine **6b**, followed by trapping with ethyl chloroformate and acidic work-up gave a 60% yield of 7,8-dimethoxy-tetrahydroisoquinolin-1-one.

GENERAL PROCEDURE FOR THE SYNTHESIS OF 7,8-DIOXYGENATED-ISOQUINOLINES

A suspension of the hydrochloride of the β-(3,4-dimethoxyphenyl)ethylamine **6b** (4 5 mmol) in dry THF in a flame-dried round-bottomed flask under an argon atmosphere was cooled to 0-5°C and a solution of nBuLi (4 5 mmol) in hexane was added After 10 min's stirring, the free amine was treated with 1 or 2 equivalents of freshly distilled trimethylsilylchloride followed by nBuLi (9 mmol), and stirring was

continued for 15 min More nBuLi (4.9 mmol) was added to the solution of the protected amine, and the reaction mixture was allowed to warm to room temperature and stirred for 16 h Dry N,N-dimethylformamide (1 to 2 eq.) was added, and after 30 min. the mixture was treated with saturated aqueous ammonium chloride solution for 15 min After evaporation of the solvent, the residue was disolved in methylene chloride and washed with water The organic phase was dried with sodium sulphate and concentrated After purification by column chromatography [silica gel, CH_2Cl_2-MeOH(2%)], the yellowish-orange isoquinoline **8a** was obtained as an oil, producing a fluorescent TLC spot under illumination at 360 nm

When ether was used as solvent the free base **6b** was the starting material.

Acknowledgements: to the Xunta de Galicia for its financial support and for a Grant to C Lamas

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6.- R L Hillard III, C A Parnell and K P.C. Vollhardt, *Tetrahedron* 39, 905 (1983)

7 - S Djuric, J Venit and P Magnus, *Tetrahedron Lett* 1787 (1981)

8 - In this experiment a compound was isolated (in 30% yield) which from its NMR and MS data appears to be the result of formylation at C-5 and subsequent dimerization It seems that the disilylazane group is unable to direct metalation to the desired C-2 position

9 - A. Brossi and S Teitel, *Helv Chim Acta* 53, 1779 (1970)

10 - Compound **6e** was obtained as follows A solution of 3-hydroxy-4-methoxy-benzaldehyde in methylene chloride containing 10% of Adogen® 464 was stirred with 2 molar equivalents of an aqueous solution of NaOH for 1 hour and treated with 5 eq of methoxymethyl chloride for 30 min The O-MOM derivative was filtered through silica gel and condensed with nitromethane in the presence of anhydrous sodium acetate and methylamine hydrochloride (r.t, 22h) The nitrostyrene obtained was then reduced by slow addition to refluxing THF containing LAH

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